

Are There Environmental Forms of Systemic Autoimmune Diseases?

Evelyn V. Hess

Division of Immunology, University of Cincinnati Medical Center, Cincinnati, Ohio USA

A large number of drugs and an increasing number of environmental agents reportedly result in the appearance of a number of autoantibodies and in many instances in the appearance of a range of autoimmune clinical syndromes. The major disorders so recognized have marked resemblances to the autoimmune disease systemic lupus erythematosus. The commonly used term is drug-induced lupus; a better term is drug-related lupus. There is considerable interest at the present time in an increasing number of environmental agents. There have been two epidemics in recent years—one in Spain to a contaminant of rapeseed oil and one in the United States to a contaminant of L-tryptophan that caused an eosinophilic myositis. It is important for physicians and others involved in health care to recognize the potential associations of these diseases of unknown cause or causes. **Key words:** autoimmunity, clinical features, drugs, environmental agents, laboratory changes, mechanisms. — *Environ Health Perspect* 107(suppl 5):709–711 (1999). <http://ehpnet1.niehs.nih.gov/docs/1999/suppl-5/709-711hess/abstract.html>

The cause or causes of the nearly 100 autoimmune disorders have in most cases not been specifically defined, although much information is available on mechanisms. First observations on a possible relationship to medications were made in 1945 when an association was noted between a lupuslike syndrome in a patient receiving sulfadiazine. There were many subsequent reports implicating sulfonamides and penicillin, again with systemic lupuslike features. In 1953, hydralazine given in the treatment of hypertension was also reported to be related to a lupuslike syndrome. These observations by Morrow et al. (1) were really the first substantially documented observations; the earlier observations were on case reports, thus leaving open the possibility that these could have been cases of idiopathic systemic lupus. The drug procainamide, which is used for the treatment of cardiac arrhythmias (2), has the best documented association with drug-related lupus (DRL) syndromes. The anti-convulsant drugs were first associated with such presentations in 1957 (3). Since that time, at least 70 pharmacologic and other agents have been associated with DRL syndromes. These include antiarrhythmic, anti-hypertensive, antipsychotic, antithyroid, antirheumatic, antibiotics, and more recently, various biologic agents.

Table 1 lists the drugs currently associated with lupus syndromes. In recent years, there has been an increasing number of associations with potential environmental factors. Clinically, many of these associated syndromes reflect other types of autoimmune disorders similar to polymyositis, scleroderma/systemic sclerosis, various vasculitides, and other clinical syndromes that do not necessarily fit under the known disease headings. We have known for many years that certain chemicals may initiate clinical

syndromes such as acute hemolytic anemias. Earlier and current observations relate various heavy metal exposures to autoimmune phenomenon and, in some cases, to very specific renal disorders.

Because of these observations, there is considerable thought about unknown environmental agents as a potential cause or causes for many autoimmune diseases and perhaps even for other disorders. However, there is no evidence that such agents cause idiopathic systemic lupus erythematosus (SLE). This article reviews the clinical similarities or differences against the more standard idiopathic autoimmune diseases and the mechanisms involved and concludes with speculations on the future.

Clinical Features

Most information contrasting idiopathic SLE with drug-related syndromes is from the studies and reports documenting where these reactions to a specific medication occur. Clinical features related to possible environmental factors are reviewed as the second part of this section. One problem is that although the American College of Rheumatology (ACR) has defined classification criteria for SLE (4) and for 11 other rheumatic diseases, criteria for drugs and environmental factors have not been determined and are still evolving. The Environmental Study Group of the ACR has proposed a set of criteria to be published in the near future.

First it should be noted that with DRL most of the observed reactions occur in the elderly population because of the higher incidence of diseases for which the specific drugs are prescribed. Reactions to the anti-convulsant drugs are seen more often in younger age groups. DRL also occurs only slightly more frequently in females than in males, and at least in the United States, it

appears more frequently in Caucasians than in African Americans. Idiopathic SLE occurs mostly in younger women and in the United States in a high proportion of African Americans.

The disease symptoms are somewhat milder, and as the potential association with a drug or medication is noted, the symptoms can often be aborted when the offending drug is stopped. Clinically, the skin, renal, and neurologic features of SLE are relatively rare in DRL. Table 2 lists the frequency of clinical and laboratory features in the two types of lupus disorders.

Laboratory Changes

Clearly, at least until now, the “ticket of admission” to diagnosis has been a positive antinuclear antibody (ANA). The laboratory profiles of idiopathic SLE and DRL are listed in Table 2. The ANA staining pattern is usually the diffuse type, and antibodies to single-stranded DNA (ssDNA) as opposed to double-stranded DNA (dsDNA) are seen with DRL. Antibodies to histones are seen very frequently with DRL and there has been considerable study of these antibodies to different histone proteins. With different drugs, there appears to be a broad array of autoantigenic epitopes to the individual histone and histone complexes. Recent work suggests that a switch from IgM to IgG isotype may precede the development of lupuslike syndromes, particularly in patients taking procainamide (5). It should also be noted that antiphospholipid antibodies and lupus anticoagulants occur in DRL. They have been found with a long list of drugs and are frequently of the IgM subclass. Other antibodies that have been reported with different drugs include lymphocytotoxic, antineutrophilic, anticytoplasmic antibodies, and antibodies to both hydralazine and procainamide metabolites.

It is appropriate to make some specific comments relative to some drugs and biologic agents. Minocycline hydrochloride, a

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Address correspondence to E.V. Hess, University of Cincinnati Medical Center, Division of Immunology, 231 Bethesda Ave., ML 0563, Cincinnati, OH 45267-0563. Telephone: (513) 558-4701. Fax (513) 558-3799. E-mail: hessev@email.uc.edu

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Table 1. Drugs associated with DRL.

Drugs definitively associated with DRL. ^a	
Chlorpromazine	
Hydralazine	
Isoniazid	
Methyldopa	
Minocycline	
Procainamide	
Quinidine	
Other drugs associated with DRL and currently in use. ^b	
Acebutolol	Methimazole
Acecaidine	Metoprolol
Allopurinol	Metrizamide
Aminoglutethimide	Minocycline
Amoproxan	Minoxidil
Anthiomaline	Nalidixic acid
Antitumor necrosis factor- α	Nitrofurantoin
Atenolol	Oxyphenisatin
Benoxaprofen	Oxyphenolol
Captopril	p-Amino salicylic acid
Carbamazepine	Penicillamine
Chlorprothixene	Penicillin
Chlorthalidone	Perazine
Cimetidine	Perphenazine
Cinnarazine	Phenelzone
Clonidine	Phenytoin
Danazol	Prazosin
Diclofenac	Primidone
1,2-Dimethyl-3-hydroxy pyridine-4-1	Prindolol
Diphenylhydantoin	Promethazine
Disopyramide	Propafenone
Enalapril	Prophythiouracil
Estrogens	Propranolol
Ethosuximide	Pyrithiazine
Ethylphenacetamide	Pyriothoxine
Gold salts	Quinine
Griseofulvin	Reserpine
Guanoxan	Spiroonolactone
Ibuprofen	Streptomycin
Interferon- α	Sulfadimethoxine
Interferon- γ	Sulfamethoxy
Interleukin-2	Sulfasalazine
Labetalol	Sulindac
Leuprolide acetate	Tetracyclines
Levodopa	Tetrazine
Levomoprazone	Thioridazine
Lithium carbonate	Timolol eyedrops
Lovastatin	Tolazamide
Mephentoin	Tolmetin
	Trimethadione

DRL, drug-related lupus. ^aSubstantial observations and studies.^bA few are single case reports but the majority represent good clinical observations.

semisynthetic tetracycline, has long been used for the treatment of the skin disorder acne vulgaris. It was first noted to be related with DRL in 1992 (6) and to the present time, an additional 76 cases have been published. Most of these cases appear to occur in young women, perhaps because they are most often being treated for acne.

A polyarthralgia or polyarthritis affecting the small joints, rather similar to rheumatoid arthritis, is a common feature. The duration of therapy has ranged from a few weeks to 10 years. Another feature of DRL is that not all of the patients have a positive ANA; antibodies to dsDNA, phospholipids and to p-ANCA antibodies have been reported (7).

Table 2. Frequency of clinical and laboratory features in idiopathic SLE and DRL.

Features	Idiopathic SLE	DRL
Constitutional	40–85	40–50
Arthralgias/arthritis	75–95	80–95
Myalgias	40–80	35–57
Rash	50–70	0–30
Lymphadenopathy	23–67	< 15
Pleurisy	42–60	0–52
Pleural effusion	16–20	0–33
Pulmonary infiltrates	0–10	5–40
Pericarditis	20–30	0–18
Hepatomegaly	10–31	0–25
Splenomegaly	9–46	0–20
Renal involvement	50	0–13 (hydralazine)
Neurologic involvement	25–70	0–2
Anemia	30–90	0–53
Leukopenia	35–66	0–33
Thrombocytopenia	20–50	0–10
Positive Coombs	18–30	0–23
Elevated ESR	50–75	60–93
Antinuclear antibodies	> 95	100
Antibodies to histones	50–70	> 95
Antibodies to dsDNA	50	< 5
Anti-Sm antibodies	25	< 5
Hypocomplementemia	40–65	0–25
Rheumatoid factor	25	20–40

Abbreviations: anti-Sm, anti-Smith; DRL, drug-related lupus; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; SLE, systemic lupus erythematosus.

Table 3. Environmental factors reported to be associated with the development of autoantibodies and lupuslike syndromes.

Hydrazines
Tartrazine
Hair dyes
Chemicals used in computer manufacturing
? Trichloroethylene
? Industrial emissions and hazardous wastes
Silica (quartz)
Paraffin/silicone
Mercury
Cadmium
Gold
L-Canavanine
Rapeseed oil, toxic oil syndrome
L-Tryptophan, eosinophilia myalgia syndrome

Environmental Agents

Since the acceptance that various drugs and medications can induce autoimmune phenomena and disease states, greater interest has focused on the potential of environmental agents to do the same. Early reports discussed the possibility of hydrazines as an inciting factor (9) and in recent years the list has grown. This area was given great impetus by two epidemics—a toxic oil syndrome in Spain due to a contaminant in rapeseed oil (10) and, more recently, in the United States, the eosinophilic myalgia syndrome related to a possible contaminant in L-tryptophan (11). The list of reported associations is given in Table 3. A dietary factor, L-canavanine, is included. This is a common amino acid in alfalfa seeds and sprouts and a relationship to a lupuslike syndrome has been described in the United States (12). The concern is that with the increasing use of health food products, other such associations may occur. It is important for physicians to be alert to these possibilities.

Confirmation of observations relating to many of these environmental factors by the use of prospective controlled studies is urgently needed. For example, the potential relationship of the onset of lupus to hair dyes has not been confirmed by more recent studies (13). Similarly, observations by Vojdani et al. (14) on immune dysregulation in workers exposed to different chemicals in computer manufacturing plants have not yet been confirmed. Various reported increased prevalence of antinuclear antibodies and lupuslike syndromes in communities exposed to well water contaminated by trichloroethylene and other chemicals in Arizona, North Georgia, and Texas await further study and confirmation.

The relationship of lupus syndromes and scleroderma to silica has been confirmed by studies in miners in Silesia (15). Data presented at this meeting have shown an association of scleroderma in South Carolina to solvent-oriented hobbies (16).

There is little need to provide any details here about the controversy relating to injection or implantation of paraffin and silicone in breast augmentation procedures. Where large-scale studies have been performed, definitive associations have not been shown. Interpretation is made even more difficult by the wide range of symptoms reported; the general term "siliconosis" has been invoked.

A detailed study of the two large confirmed environmental outbreaks is recommended to the reader. The first of these was the outbreak in Spain in 1981 in over 35,000 people related to the ingestion of denatured rapeseed oil (10). Again, what is striking is the very long list of nonspecific symptoms—fever, malaise, lung involvement, muscle/joint involvement, and the eventual appearance of

Biologic Agents

Biologic agents are being used increasingly for the treatment of malignancies, infections, and many autoimmune diseases. Such agents include many cytokines such as interferon- α , - β , and - γ , interleukin-2, and more recently, antitumor necrosis factor- α used in the treatment of rheumatoid arthritis. Many antibodies have been reported including positive ANAs and anti-DNA antibodies but also clinical features of autoimmune thyroid disease, autoimmune hemolytic anemia, and thrombocytopenia, lupuslike syndromes, pernicious anemia, and vasculitis with the use of these antibodies (8).

sclerodermalike disease, lupuslike disease, peripheral neuropathies, and Sjögren-like syndromes. Long-term follow-up has shown the persistence of disease in about 10% of those originally affected. Similarly, the eosinophilia myalgia syndrome first described by Edison et al. (11) in 1989 had a similar range of symptoms and was characterized by a marked increase in peripheral blood eosinophils and muscle disease confirmed by muscle biopsy. On follow-up, many of these patients developed a scleroderma-like condition, lung involvement, and sensory neuropathies, again similar to that in the Spanish outbreak. ANAs and antihistone antibodies were present, but antibodies to different nuclear and cytoplasmic antigens were negative.

It is of note that a number of other compounds can also give rise to an eosinophilic myalgia or myositis syndrome. These include Tranilast (a mast cell stabilizer), sulfisoxazole, penicillamine, simethicone, phenytoin and alcohol.

Heavy Metals

It is well known that chronic exposure to a number of metals such as mercury, gold, and cadmium can induce autoantibodies and clinically an immune complex-mediated glomerulonephritis. Most of these observations have been in animals, although there are now some reports in humans. The latter have occurred mainly in patients exposed to mercury through the use of skin-lightening creams (17). The immune deposition of immunoglobulins has been noted in patients receiving chronic administration of gold.

Possible Mechanisms and the Future

The mechanisms by which these drugs and/or their metabolites, the chemicals and their breakdown products, and the other environmental factors and their various structures are as diverse as the entire immune system itself. Literally hundreds of papers have examined the drugs and other factors listed in this article and about every conceivable effect has been noted. It is not possible to define a specific role or pathway that would result in the

varied immunologic and clinical syndromes seen. For drugs such as hydralazine and procainamide, the specific metabolites that react with specific immune cells have been well demonstrated (18,19). Other proposed mechanisms for a number of the compounds include the possibility of cross-reactive antigens, interference with various tolerance mechanisms, potential alteration of DNA by the drugs or their metabolites, and the role of the genetics of the various metabolic pathways of the compounds, in particular the P450 enzyme system. Studies of the actual drug structures for any commonality have not been very productive. Basically, the various drugs often fall under three different structural groups: hydrazines, aromatic amines, and phenols. Studies to date of the various environmental factors again have not revealed any major commonality.

Another factor that has to be considered in humans and experimental animals is the possible inciting or potentiating effect of infectious agents. Myxoviruses, retroviruses, measles, rubella, parainfluenza, Epstein-Barr, Type C oncoviruses, and Type C retroviruses could all play a role and must be considered when looking at mechanisms of cross-reactive antigens (20). Among the bacteria under consideration are streptococcal cell wall products, lipopolysaccharides, and adjuvant components.

The genetics of the immune system in autoimmune diseases and phenomena is increasingly complex. It would appear that for any one compound or environmental agent, genetic factors may differ. There is also the added complication of the genetics of the host response as manifested in the expression of different disease states. However complicated, such studies should continue and be supported, as can be seen from the example of the specific genetic association of HLA-DP.B1 glutamate in beryllium-exposed workers (21). The National Research Council established a program in 1991 to define biologic markers in immunotoxicology. This and many other aspects of the National Toxicology Program should be strongly supported and is a recommendation of this conference.

REFERENCES AND NOTES

- Morrow JD, Schroeder HA, Perry HM Jr. Studies on the control of hypertension by Hyphex. II: Toxic reactions and side effects. *Circulation* 8:829-839 (1953).
- Ladd AT. Procainamide-induced lupus erythematosus. *N Engl J Med* 267:1357-1358 (1962).
- Lindqvist T. Lupus erythematosus disseminatus after administration of mesantoin. Report of two cases. *Acta Med Scand* 158:131 (1957).
- Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25:1271-1277 (1982).
- Mongey AB, Adams LE, Donovan-Brand R, Thomas TJ, Hess EV. Serologic evaluation of patients receiving procainamide. *Arthritis Rheum* 35:219-222 (1992).
- Matsuura T, Shimizu Y, Fujimoto H, Miyazaki T, Kano S. Minocycline-related lupus [Letter]. *Lancet* 340:1553 (1992).
- Dunphy J, Rands A, McHugh NJ. Antimyeloperoxidase antibodies in minocycline-induced lupus syndrome [Abstract]. *Br J Rheumatol* 36(suppl 1):5 (1997).
- Feldman M. TNF blockade in rheumatoid arthritis. *Prog. AAI, CIS, AAA Annual Meeting*, February 1997, San Francisco, California.
- Reidenberg MM, Durant PJ, Harris RA, DeBoccardo G, Lahita R, Stenzel KH. Lupus erythematosus-like disease due to hydralazine. *Am J Med* 75:365-370 (1983).
- Alonso-Ruiz A, Zea-Mendoza AC, Salazar-Vallinas JM, Rocamora-Ripoli A, Beltran-Gutierrez J. Toxic oil syndrome: a syndrome with features overlapping those of various forms of scleroderma. *Semin Arthritis Rheum* 15:200-212 (1986).
- Edison M, Philen RM, Sewell CM, Voorhees R, Kilbourne EM. L-Tryptophan and eosinophilic-myalgia syndrome in New Mexico. *Lancet* 335:645-648 (1990).
- Manilow MR, Bardana EJ Jr, Goodnight SH. Pancytopenia during ingestion of alfalfa seeds [Letter]. *Lancet* 1:615 (1981).
- Petri M, Allbritton J. Hair product use in systemic lupus erythematosus—a case controlled study. *Arthritis Rheum* 35:625-629 (1992).
- Vojdani A, Choneum M, Brautbar N. Immune alteration associated with exposure to toxic chemicals. *Toxicol Ind Health* 8:239-254 (1992).
- Conrad K, Mehlhorn J, Luthke K, Dorner T, Frank KH. Systemic lupus erythematosus after heavy exposure to quartz dust in uranium mines: clinical and serological characteristics. *Lupus* 5:62-69 (1996).
- Nieter PJ, Sutherland SE, Silver RM, Pandey JP, Knapp RG, Hoel DG, Dosemeci M. Solvent-oriented hobbies and the risk of systemic sclerosis. *Arthritis Rheum* 35:1111-1118 (1998).
- Lindqvist KJ, Makene WJ, Shaba JD, Nantulya V. Immunofluorescence and electron microscopic studies of kidney biopsies from patient with nephrotic syndrome, possibly induced by skin lightening creams containing mercury [Abstract]. *E Afr Med* 51:168 (1974).
- Litwin A, Adams LE, Zimmer H, Hess EV. Immunologic effects of hydralazine in hypertensive patients. *Arthritis Rheum* 24:1074-1077 (1981).
- Adams LE, Balakrishnan K, Roberts SM, Belcher R, Mongey A-B, Thomas TJ, Hess EV. Genetic, immunologic and biotransformation studies of patients on procainamide. *Lupus* 2:89-98 (1993).
- Hess EV. Minocycline and autoimmunity. *Clin Exp Rheum* 16:519-521 (1998).
- Richeldi L, Sorrentino R, Saltini C. DP-B1 glutamate 69: a genetic marker of beryllium disease. *Science* 262:242-244 (1993).